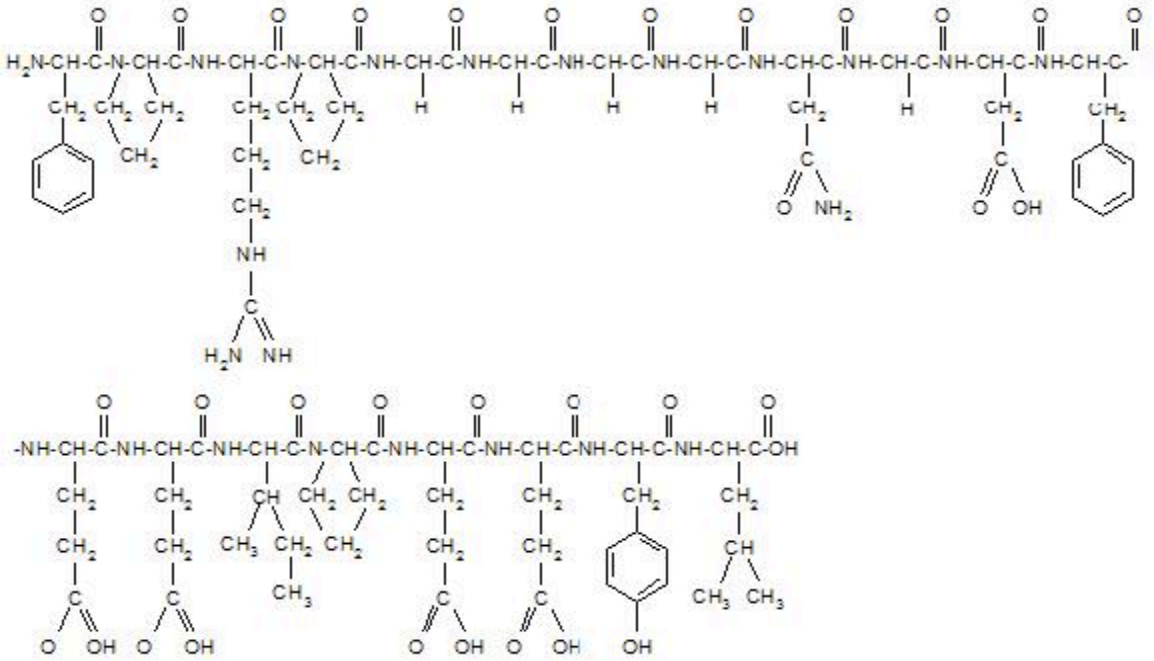
ANGIOMAX - bivalirudin injection, powder, lyophilized, for solution
The Medicines Company

DESCRIPTION

Angiomax® (bivalirudin) is a specific and reversible direct thrombin inhibitor. The active substance is a synthetic, 20 amino acid peptide. The chemical name is D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate (Figure 1). The molecular weight of Angiomax is 2180 daltons (anhydrous free base peptide). Angiomax is supplied in single-use vials as a white lyophilized cake, which is sterile. Each vial contains 250 mg bivalirudin, 125 mg mannitol, and sodium hydroxide to adjust the pH to 5-6 (equivalent of approximately 12.5 mg sodium). When reconstituted with Sterile Water for Injection the product yields a clear to opalescent, colorless to slightly yellow solution, pH 5-6.

Figure 1. Structural Formula for Bivalirudin



CLINICAL PHARMACOLOGY

General:

Angiomax directly inhibits thrombin by specifically binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Thrombin is a serine proteinase that plays a central role in the thrombotic process, acting to cleave fibrinogen into fibrin monomers and to activate Factor XIII to Factor XIIIa, allowing fibrin to develop a covalently cross-linked framework which stabilizes the thrombus; thrombin also activates Factors V and VIII, promoting further thrombin generation, and activates platelets, stimulating aggregation and granule release. The binding of Angiomax to thrombin is reversible as thrombin slowly cleaves the Angiomax-Arg_3-Pro_4 bond, resulting in recovery of thrombin active site functions.

In *in vitro* studies, Angiomax inhibited both soluble (free) and clot-bound thrombin, was not neutralized by products of the platelet release reaction, and prolonged the activated partial thromboplastin time (aPTT), thrombin time (TT), and prothrombin time (PT) of normal human plasma in a concentration-dependent manner. The clinical relevance of these findings is unknown.

Pharmacokinetics:

Angiomax exhibits linear pharmacokinetics following intravenous (IV) administration to patients undergoing percutaneous transluminal coronary angioplasty (PTCA). In these patients, a mean steady state Angiomax concentration of 12.3 ± 1.7 mcg/mL is achieved following an IV bolus of 1 mg/kg and a 4-hour 2.5 mg/kg/h IV infusion. Angiomax is cleared from plasma by a combination of renal mechanisms and proteolytic cleavage, with a half-life in patients with normal renal function of 25 min. The disposition of Angiomax was studied in PTCA patients with mild and moderate renal impairment and in patients with severe renal impairment. Drug elimination was related to glomerular filtration rate (GFR). Total body clearance was similar for patients with normal renal function and with mild renal impairment (60-89 mL/min). Clearance was reduced approximately 20% in patients with moderate and severe renal impairment and was reduced approximately 80% in dialysis-dependent patients. See Table 1 for pharmacokinetic

parameters. For patients with renal impairment the activated clotting time (ACT) should be monitored. For dosing instructions, refer to the **DOSAGE AND ADMINISTRATION** section. Angiomax is hemodialyzable. Approximately 25% is cleared by hemodialysis. Angiomax does not bind to plasma proteins (other than thrombin) or to red blood cells.

Table 1. PK Parameters in patients with renal impairment*

Renal Function (GFR, mL/min)	**Clearance (mL/min/kg)**	**Half-life (min)**
Normal renal function (≥90 mL/min)	3.4	25
Mild renal impairment (60-89 mL/min)	3.4	22
Moderate renal impairment (30-59 mL/min)	2.7	34
Severe renal impairment (10-29 mL/min)	2.8	57
Dialysis-dependent patients (off dialysis)	1.0	3.5 hours

***The ACT should be monitored in renally-impaired patients.

Pharmacodynamics:

In healthy volunteers and patients (with ≥ 70% vessel occlusion undergoing routine angioplasty), Angiomax® (bivalirudin) exhibits linear dose- and concentration-dependent anticoagulant activity as evidenced by prolongation of the ACT, aPTT, PT, and TT. Intravenous administration of Angiomax produces an immediate anticoagulant effect. Coagulation times return to baseline approximately 1 hour following cessation of Angiomax administration.

In 291 patients with ≥70% vessel occlusion undergoing routine angioplasty, a positive correlation was observed between the dose of Angiomax and the proportion of patients achieving ACT values of 300 sec or 350 sec. At an Angiomax dose of 1.0 mg/kg IV bolus plus 2.5 mg/kg/h IV infusion for 4 hours, followed by 0.2 mg/kg/h, all patients reached maximal ACT values >300 sec.

CLINICAL TRIALS

Angiomax has been evaluated in five randomized, controlled interventional cardiology trials reporting 11,422 patients. Stents were deployed in 6062 of the patients in these trials – mainly in trials performed since 1995. Percutaneous transluminal coronary angioplasty (PTCA), atherectomy or other procedures were performed in the remaining patients.

REPLACE-2 Trial:

This was a randomized double-blind multicenter study reporting 6002 (intent-to-treat) patients undergoing percutaneous coronary intervention (PCI). Patients were randomized to treatment with Angiomax with the “provisional” use of platelet glycoprotein IIb/IIIa inhibitor (GPI) or heparin plus planned use of GPI. GPIs were added on a “provisional” basis to patients who were randomized to Angiomax in the following circumstances:

1. decreased TIMI flow (0 to 2) or slow reflow;
2. dissection with decreased flow;
3. new or suspected thrombus;
4. persistent residual stenosis;
5. distal embolization;
6. unplanned stent;
7. suboptimal stenting;
8. side branch closure;
9. abrupt closure; clinical instability; and
10. prolonged ischemia.

During the study, one or more of these circumstances occurred in 12.7% of patients in the Angiomax with provisional GPI arm. GPIs were administered to 7.2% of patients in the Angiomax with provisional GPI arm (62.2% of eligible patients).
Patients ranged in age from 25-95 years (median 63); weight ranged from 35-199 kg (median 85.5): 74.4% were male and 25.6% were female. Indications for PCI included unstable angina (35% of patients), myocardial infarction within 7 days prior to intervention (8% of patients), stable angina (25%) and positive ischemic stress test (24%). Stents were deployed in 85% of patients. Ninety-nine percent of patients received aspirin and 86% received thienopyridines prior to study treatment.
Angiomax was administered as a 0.75 mg/kg bolus followed by a 1.75 mg/kg/h infusion for the duration of the procedure. At investigator discretion, the infusion could be continued following the procedure for up to 4 hours. The median infusion duration was 44 min. Heparin was administered as a 65 U/kg bolus. GPIs (either abciximab or eptifibatide) were given according to manufacturers' instructions. Both randomized groups could be given "provisional" treatments during the PCI at investigator discretion, but under double-blind conditions. "Provisional" treatment with GPI was requested in 5.2% of patients randomized to heparin plus GPI (they were given placebo) and 7.2% patients randomized to Angiomax with provisional GPI (they were given abciximab or eptifibatide according to pre-randomization investigator choice and patient stratification).

The activated clotting time (ACT – measured by a Hemochron® device) was measured 5 min after the first bolus of study medication. The percent of patients reaching protocol-specified levels of anticoagulation was greater in the Angiomax with provisional GPI group than in the heparin plus GPI group. For patients randomized to Angiomax® (bivalirudin) with provisional GPI, the median 5 min ACT was 358 sec (interquartile range 320-400 sec) and the ACT was <225 sec in 3%. For patients randomized to heparin plus GPI, the median 5 min ACT was 317 sec (interquartile range 263-373 sec) and the ACT was <225 sec in 12%. At the end of the procedure, median ACT values were 334 sec (Angiomax group) and 276 sec (heparin plus GPI group).
For the composite endpoint of death, MI, or urgent revascularization adjudicated under double-blind conditions, the frequency was higher (7.6%) (95% confidence interval 6.7%-8.6%) in the Angiomax with "provisional" GPI arm when compared to the heparin plus GPI arm (7.1%) (95% confidence interval 6.1%-8.0%). However, major hemorrhage was reported significantly less frequently in the Angiomax with provisional GPI arm (2.4%) compared to the heparin plus GPI arm (4.1%). Study outcomes are shown in Table 2.
At 12 months follow-up, mortality was 1.9% among patients randomized to Angiomax with "provisional" GPIs and 2.5% among patients randomized to heparin plus GPI.
Table 2. Incidences of Clinical Endpoints at 30 Days for REPLACE-2, a Randomized Double-blind Clinical Trial

Intent-to-treat population	**ANGIOMAX with "Provisional" GPI** n=2994	**HEPARIN+GPI** n=3008
Efficacy Endpoints		
Death, MI, or urgent revascularization	7.6%	7.1%
Death	0.2%	0.4%
MI	7.0%	6.2%
Urgent revascularization	1.2%	1.4%
Safety Endpoint		
Major hemorrhage*,†	2.4%	4.1%

***** Defined as intracranial bleeding, retroperitoneal bleeding, a transfusion of ≥2 units of blood/blood products, a fall in hemoglobin >4 g/dL, whether or not bleeding site is identified, spontaneous or non-spontaneous blood loss with a decrease in hemoglobin >3 g/dL.
† p-value <0.001 between groups.

Bivalirudin Angioplasty Trial (BAT):

Angiomax® (bivalirudin) was evaluated in patients with unstable angina undergoing PTCA in two randomized, double-blind, multicenter studies with identical protocols. Patients must have had unstable angina defined as: (1) a new onset of severe or accelerated angina or rest pain within the month prior to study entry or (2) angina or ischemic rest pain which developed between four hours and two weeks after an acute myocardial infarction (MI). Overall, 4312 patients with unstable angina, including 741 (17%) patients with post-MI angina, were treated in a 1:1 randomized fashion with Angiomax or heparin. Patients ranged in age from 29-90 (median 63) years, their weight was a median of 80 kg (39-120 kg), 68% were male, and 91% were Caucasian. Twenty-three percent of patients were treated with heparin within one hour prior to randomization. All patients were administered aspirin 300-325 mg prior to PTCA and daily thereafter. Patients randomized to Angiomax were started on an intravenous infusion of Angiomax (2.5 mg/kg/h). Within 5 min after starting the infusion, and prior to PTCA, a 1 mg/kg loading dose was administered as an intravenous bolus. The infusion was continued for 4 hours, then the infusion was changed under double-blinded conditions to Angiomax (0.2 mg/kg/h) for up to an additional 20 hours (patients received this infusion for an average of 14 hours). The ACT was checked at 5 min and at 45 min following commencement. If on either occasion the ACT was <350 sec, an additional double-blinded bolus of placebo was administered. The Angiomax dose was not titrated to ACT. Median ACT values were: ACT in sec (5^{th} percentile-95^{th}

percentile): 345 sec (240-595 sec) at 5 min and 346 sec (range 269-583 sec) at 45 min after initiation of dosing. Patients randomized to heparin were given a loading dose (175 IU/kg) as an intravenous bolus 5 min before the planned procedure, with immediate commencement of an infusion of heparin (15 IU/kg/h). The infusion was continued for 4 hours. After 4 hours of infusion, the heparin infusion was changed under double-blinded conditions to heparin (15 IU/kg/h) for up to 20 additional hours. The ACT was checked at 5 min and at 45 min following commencement. If on either occasion the ACT was <350 sec, an additional double-blind bolus of heparin (60 IU/kg) was administered. Once the target ACT was achieved for heparin patients, no further ACT measurements were performed. All ACTs were determined with the Hemochron® device. The protocol allowed use of open-label heparin at the discretion of the investigator after discontinuation of blinded study medication, whether or not an endpoint event (procedural failure) had occurred. The use of open-label heparin was similar between Angiomax and heparin treatment groups (about 20% in both groups).

The studies were designed to demonstrate the safety and efficacy of Angiomax in patients undergoing PTCA as a treatment for unstable angina as compared with a control group of similar patients receiving heparin during and up to 24 hours after initiation of PTCA. The primary protocol endpoint was a composite endpoint called procedural failure, which included both clinical and angiographic elements measured during hospitalization. The clinical elements were: the occurrence of death, MI, or urgent revascularization, adjudicated under double-blind conditions. The angiographic elements were: impending or abrupt vessel closure. The protocol-specified safety endpoint was major hemorrhage.
The median duration of hospitalization was 4 days for both the Angiomax and heparin treatment groups. The rates of procedural failure were similar in the Angiomax and heparin treatment groups. Study outcomes are shown in Table 3.
Table 3. Incidences of In-hospital Clinical Endpoints in BAT Trial Occurring within 7 Days

All Patients	**Angiomax** n=2161	**Heparin** n=2151
Efficacy Endpoints	7.9%	9.3%
Procedural failure*		
Death, MI, revascularization	6.2%	7.9%
Death	0.2%	0.2%
MI†	3.3%	4.2%
Revascularization‡	4.2%	5.6%
Safety Endpoint		
Major hemorrhage§	3.5%	9.3%

***** The protocol-specified primary endpoint (a composite of death or MI or clinical deterioration of cardiac origin requiring revascularization or placement of an aortic balloon pump or angiographic evidence of abrupt vessel closure).
† Defined as: Q-wave MI; CK-MB elevation ≥2xULN, new ST- or T-wave abnormality, and chest pain ≥30 min; OR new LBBB with chest pain ≥30 min and/or elevated CK-MB enzymes; OR elevated CK-MB and new ST- or T-wave abnormality without chest pain; OR elevated CK-MB.
‡ Defined as: any revascularization procedure, including angioplasty, CABG, stenting, or placement of an intra-aortic balloon pump.
§ Defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in hemoglobin ≥3 g/dL or leading to a transfusion of ≥2 units of blood.

AT-BAT Trial:
This was a single-group open-label study which enrolled 51 patients with heparin-induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. Evidence for the diagnosis of HIT/HITTS was based on a clinical history of a decrease of platelets in patients after heparin administration [new diagnosis or history of clinically suspected or objectively documented HIT/HITTS, defined as either: 1) HIT: positive heparin-induced platelet aggregation (HIPA) or other functional assay where the platelet count has decreased to <100,000/mL (minimum 30% from prior to heparin), or has decreased to <150,000/mL (minimum 40% from prior to heparin), or has decreased as above within hours of receiving heparin in a patient with a recent, previous exposure to heparin; 2) HITTS: thrombocytopenia as above plus arterial or venous thrombosis diagnosed by physician examination/laboratory and/or appropriate imaging studies]. Patients ranged in age from 48-89 years (median 70); weight ranged from 42-123 kg (median 76); 50% were male and 50% were female. Angiomax was administered as either 1.0 mg/kg bolus followed by 2.5 mg/kg/h (high dose in 28 patients) or 0.75 mg/kg bolus followed by a 1.75 mg/kg/h infusion (lower dose in 25 patients) for up to 4 hours. Ninety-eight percent of patients received aspirin, 86% received clopidogrel and 19% received GPIs.
The median ACT values at the time of device activation were 379 sec (high dose) and 317 sec (lower dose). Following the procedure, 48 of the 51 patients (94%) had TIMI grade 3 flow and stenosis <50%. One patient died during a bradycardic episode 46 hours after successful PCI, another patient required surgical revascularization, and one patient experienced no flow requiring a temporary intra-aortic balloon.
Two of the fifty-one patients with the diagnosis of HIT/HITTS developed thrombocytopenia after receiving bivalirudin and GPIs.

INDICATIONS AND USAGE

Angiomax is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

Angiomax with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as listed in the **CLINICAL TRIALS REPLACE-2** section is indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).

Angiomax is indicated for patients with, or at risk of, HIT/HITTS undergoing PCI.

Angiomax is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

The safety and effectiveness of Angiomax have not been established in patients with acute coronary syndromes who are not undergoing PTCA or PCI.

CONTRAINDICATIONS

Angiomax is contraindicated in patients with:

- active major bleeding;

- hypersensitivity to Angiomax or its components.

WARNINGS

Angiomax is not intended for intramuscular administration. Although most bleeding associated with the use of Angiomax in PCI occurs at the site of arterial puncture, hemorrhage can occur at any site. An unexplained fall in blood pressure or hematocrit, or any unexplained symptom, should lead to serious consideration of a hemorrhagic event and cessation of Angiomax administration.

An increased risk of thrombus formation has been associated with the use of Angiomax in gamma brachytherapy, including fatal outcomes.

There is no known antidote to Angiomax. Angiomax is hemodialyzable (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

PRECAUTIONS

General:

Caution should be used when Angiomax is used as the anti-thrombin during brachytherapy procedures. Operators are advised to maintain meticulous catheter technique, with frequent aspiration and flushing, paying special attention to minimizing conditions of stasis within the catheter or vessels (see **WARNINGS** and **Post-marketing Events)**.

Drug Interactions:

Angiomax does not exhibit binding to plasma proteins (other than thrombin) or red blood cells.

In clinical trials in patients undergoing PTCA/PCI, co-administration of Angiomax with heparin, warfarin, thrombolytics or glycoprotein IIb/IIIa inhibitors was associated with increased risks of major bleeding events compared to patients not receiving these concomitant medications. There is no experience with co-administration of Angiomax and plasma expanders such as dextran. Angiomax should be used with caution in patients with disease states associated with an increased risk of bleeding.

Pediatric Use:

The safety and effectiveness of Angiomax in pediatric patients have not been established.

Immunogenicity/Re-exposure:

In *in vitro* studies, Angiomax exhibited no platelet aggregation response against sera from patients with a history of HIT/HITTS. Among 494 subjects who received Angiomax in clinical trials and were tested for antibodies, 2 subjects had treatment-emergent positive bivalirudin antibody tests. Neither subject demonstrated clinical evidence of allergic or anaphylactic reactions and repeat testing was not performed. Nine additional patients who had initial positive tests were negative on repeat testing.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of Angiomax. Angiomax displayed no genotoxic potential in the *in vitro* bacterial cell reverse mutation assay (Ames test), the *in vitro* Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the *in vitro* human lymphocyte chromosomal aberration assay, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay, and the *in vivo* rat micronucleus assay. Fertility and general reproductive performance in rats were unaffected by subcutaneous doses of Angiomax up to 150 mg/kg/day, about 1.6 times the dose on a body surface area basis (mg/m^2) of a 50 kg person given the maximum recommended dose of 15 mg/kg/day.

Pregnancy:

Angiomax® (bivalirudin) is intended for use with aspirin (see **INDICATIONS AND USAGE**). Because of possible adverse effects on the neonate and the potential for increased maternal bleeding, particularly during the third trimester, Angiomax and aspirin should be used together during pregnancy only if clearly needed.

Pregnancy Category B:
Teratogenicity studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day, (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area). These studies revealed no evidence of impaired fertility or harm to the fetus attributable to Angiomax. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:
It is not known whether Angiomax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Angiomax is administered to a nursing woman.

Geriatric Patients:
In studies of patients undergoing PCI, 44% were ≥65 years of age, and 12% were >75 years old. Elderly patients experienced more bleeding events than younger patients. Patients treated with Angiomax experienced fewer bleeding events in each age stratum, compared to heparin.

ADVERSE REACTIONS

Bleeding:
In 6010 patients undergoing PCI treated in the REPLACE-2 trial, Angiomax patients exhibited statistically significantly lower rates of bleeding, transfusions, and thrombocytopenia as noted in Table 4.
Table 4. Major Hematologic Outcomes REPLACE-2 Study (Safety Population)

	ANGIOMAX with "Provisional" GPI[*] (n=2914)	**HEPARIN+GPI (n=2987)**	**p-value**
Protocol defined major hemorrhage[†] (%)	2.3%	4.0%	<0.001
Protocol defined minor hemorrhage[‡] (%)	13.6%	25.8%	<0.001
TIMI defined bleeding[§]			
-Major	0.6%	0.9%	0.259
-Minor	1.3%	2.9%	<0.001
Non-access site bleeding			
-Retroperitoneal bleeding	0.2%	0.5%	0.069
-Intracranial bleeding	<0.1%	0.1%	1.0
Access site bleeding			
-Sheath site bleeding	0.9%	2.4%	<0.001
Thrombocytopenia[¶]			
<100,000/mm[‡]	0.7%	1.7%	<0.001
<50,000/mm[‡]	0.3%	0.6%	0.039
Transfusions			
-RBC	1.3%	1.9%	0.08
-Platelets	0.3%	0.6%	0.095

*****GPIs were administered to 7.2% of patients in the Angiomax with provisional GPI group.
† Defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, a transfusion of ≥2 units of blood/ blood products, a fall in hemoglobin >4 g/dL, whether or not bleeding site is identified, spontaneous or non-spontaneous blood loss with a decrease in hemoglobin >3 g/dL.
‡Defined as observed bleeding that does not meet the criteria for major hemorrhage.
§ TIMI major bleeding is defined as: intracranial, or a fall in adjusted Hgb >5 g/dL or Hct of >15%; TIMI minor bleeding is defined as a fall in adjusted Hgb of 3 to <5 g/dL or a fall in adjusted Hct of 9 to <15%, with a bleeding site such as hematuria, hematemesis, hematomas, retroperitoneal bleeding or a decrease in Hgb of >4 g/dL with no bleeding site.
¶ If <100,000 and >25% reduction from baseline, or <50,000.

In 4312 patients undergoing PTCA for treatment of unstable angina in 2 randomized, double-blind studies comparing Angiomax to heparin, Angiomax patients exhibited lower rates of major bleeding and lower requirements for blood transfusions. The incidence of major bleeding is presented in Table 5. The incidence of major bleeding was lower in the Angiomax group than in the heparin group.

Table 5. Major Bleeding and Transfusions in BAT Trial: All Patients*

	ANGIOMAX n=2161	**HEPARIN n=2151**
No. (%) Patients with Major Hemorrhage†	79 (3.7)	199 (9.3)
- with ≥3 g/dL fall in Hgb	41 (1.9)	124 (5.8)
- with ≥5 g/dL fall in Hgb	14 (0.6)	47 (2.2)
- Retroperitoneal bleeding	5 (0.2)	15 (0.7)
- Intracranial bleeding	1 (<0.1)	2 (<0.1)
- Required transfusion	43 (2.0)	123 (5.7)

***** No monitoring of ACT (or PTT) was done after a target ACT was achieved.
† Major hemorrhage was defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in hemoglobin ≥3 g/dL or leading to a transfusion of ≥2 units of blood. This table includes data from the entire hospitalization period.

In the AT-BAT study, 1 patient who did not undergo PCI had major bleeding during CABG on the day following angiography, 9 patients had minor bleeding (mostly due to access site bleeding), and 2 patients developed moderate thrombocytopenia.

Other Adverse Events:

Adverse events observed in clinical trials are similar between the Angiomax® (bivalirudin)-treated patients and the control groups. Adverse events seen are those typical of PCI trials, see Tables 6 and 7.

Table 6. Adverse Events Other Than Bleeding Occurring In ≥ 5% Of Patients In Either Treatment Group In BAT Trial

EVENT	**Treatment Group**	
	ANGIOMAX n=2161	**HEPARIN n=2151**
	Number of Patients (%)	
Cardiovascular		
Hypotension	262 (12)	371 (17)
Hypertension	135 (6)	115 (5)
Bradycardia	118 (5)	164 (8)
Gastrointestinal		
Nausea	318 (15)	347 (16)
Vomiting	138 (6)	169 (8)
Dyspepsia	100 (5)	111 (5)
Genitourinary		
Urinary retention	89 (4)	98 (5)
Miscellaneous		
Back pain	916 (42)	944 (44)
Pain	330 (15)	358 (17)
Headache	264 (12)	225 (10)

Injection site pain	174 (8)	274 (13)
Insomnia	142 (7)	139 (6)
Pelvic pain	130 (6)	169 (8)
Anxiety	127 (6)	140 (7)
Abdominal pain	103 (5)	104 (5)
Fever	103 (5)	108 (5)
Nervousness	102 (5)	87 (4)

Serious, non-bleeding adverse events were experienced in 2% of 2161 Angiomax-treated patients and 2% of 2151 heparin-treated patients. The following individual serious non-bleeding adverse events were rare (>0.1% to <1%) and similar in incidence between Angiomax- and heparin-treated patients. These events are listed by body system: *Body as a Whole*: fever, infection, sepsis; *Cardiovascular*: hypotension, syncope, vascular anomaly, ventricular fibrillation; *Nervous*: cerebral ischemia, confusion, facial paralysis; *Respiratory*: lung edema; *Urogenital*: kidney failure, oliguria.
In the double-blind, randomized REPLACE-2 trial comparing Angiomax with "provisional" GPI to Heparin plus GPI described above similar adverse events were reported in both treatment groups:

Table 7. Adverse Events Other Than Bleeding Occurring in ≥2% of Patients in Either Treatment Group in REPLACE-2

EVENT	**TREATMENT GROUP**	
	ANGIOMAX with "Provisional" GPI	**HEPARIN+GPI**
	n=2914	**n=2987**
	Number of Patients (%)	
Cardiovascular		
Hypotension	91 (3.1)	120 (4.0)
Angina pectoris	155 (5.3)	156 (5.2)
Gastrointestinal		
Nausea	86 (3.0)	96 (3.2)
Miscellaneous		
Back pain	268 (9.2)	263 (8.8)
Pain	98 (3.4)	72 (2.4)
Chest pain	68 (2.3)	69 (2.3)
Headache	75 (2.6)	83 (2.8)
Injection site pain	80 (2.7)	80 (2.7)

In the AT-BAT study, 1 patient died during a bradycardic episode 46 hours after a successful PCI, another patient required surgical revascularization, and 1 patient experienced no reflow requiring a temporary intra-aortic balloon. Two of the fifty-one patients with the diagnosis of HIT/HITTS developed thrombocytopenia after receiving bivalirudin and GPIs.

Post-marketing Events:
The following events have been reported: fatal bleeding; hypersensitivity and allergic reactions including very rare reports of anaphylaxis; thrombus formation during PCI with and without intracoronary brachytherapy, including reports of fatal outcomes.

OVERDOSAGE

Single bolus doses of Angiomax® (bivalirudin) up to 7.5 mg/kg have been reported without associated bleeding or other adverse events. Discontinuation of Angiomax leads to a gradual reduction in anticoagulant effects due to metabolism of the drug. In cases of overdosage, treatment with Angiomax should be immediately discontinued and the patient monitored closely for signs of bleeding. Angiomax is hemodialyzable (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**). There is no known antidote to Angiomax.

DOSAGE AND ADMINISTRATION

The recommended dose of Angiomax is an intravenous (IV) bolus dose of 0.75 mg/kg. This should be followed by an infusion of 1.75 mg/kg/h for the duration of the PCI procedure. Five min after the bolus dose has been administered, an ACT should be performed and an additional bolus of 0.3 mg/kg should be given if needed. GPI administration should be considered in the event that any of the conditions listed in **CLINICAL TRIALS REPLACE-2** is present. The recommended dose of Angiomax in patients with HIT/HITTS

undergoing PCI is an IV bolus dose of 0.75 mg/kg. This should be followed by a continuous infusion at a rate of 1.75 mg/kg/h for the duration of the procedure.
Continuation of the Angiomax infusion following PCI for up to 4 hours post-procedure is optional, at the discretion of the treating physician. After four hours, an additional IV infusion of Angiomax may be initiated at a rate of 0.2 mg/kg/h for up to 20 hours, if needed. Angiomax is intended for use with aspirin (300-325 mg daily) and has been studied only in patients receiving concomitant aspirin.

Special populations

Renal Impairment:
The infusion dose of Angiomax may need to be reduced, and anticoagulant status monitored in patients with renal impairment. Patients with moderate renal impairment (30-59 mL/min) should receive 1.75 mg/kg/h. If the creatinine clearance is less than 30 mL/min, reduction of the infusion rate to 1.0 mg/kg/h should be considered. If a patient is on hemodialysis, the infusion should be reduced to 0.25 mg/kg/h. No reduction in the bolus dose is needed. See Table 1 in **CLINICAL PHARMACOLOGY** for details regarding the half-life in patients with renal impairment.

Instructions for Administration:
Angiomax is intended for intravenous injection and infusion after dilution. To each 250 mg vial add 5 mL of Sterile Water for Injection, USP. Gently swirl until all material is dissolved. Each reconstituted vial should be further diluted in 50 mL of 5% Dextrose in Water or 0.9% Sodium Chloride for Injection to yield a final concentration of 5 mg/mL (e.g., 1 vial in 50 mL; 2 vials in 100 mL; 5 vials in 250 mL). The dose to be administered is adjusted according to the patient's weight, see Table 8.
If the low-rate infusion is used after the initial infusion, a lower concentration bag should be prepared. In order to prepare this bag, reconstitute the 250 mg vial with 5 mL of Sterile Water for Injection, USP. Gently swirl until all material is dissolved. Each reconstituted vial should be further diluted in 500 mL of 5% Dextrose in Water or 0.9% Sodium Chloride for Injection to yield a final concentration of 0.5 mg/mL. The infusion rate to be administered should be selected from the right-hand column in Table 8.
Table 8. Dosing Table

	Using 5 mg/mL Concentration		**Using 0.5 mg/mL Concentration**
Weight (kg)	**Bolus (0.75 mg/kg) (mL)**	**Infusion (1.75 mg/kg/h) (mL/h)**	**Subsequent Low-rate Infusion (0.2 mg/kg/h) (mL/h)**
43-47	7	16	18
48-52	7.5	17.5	20
53-57	8	19	22
58-62	9	21	24
63-67	10	23	26
68-72	10.5	24.5	28
73-77	11	26	30
78-82	12	28	32
83-87	13	30	34
88-92	13.5	31.5	36
93-97	14	33	38
98-102	15	35	40
103-107	16	37	42
108-112	16.5	38.5	44
113-117	17	40	46
118-122	18	42	48
123-127	19	44	50
128-132	19.5	45.5	52
133-137	20	47	54
138-142	21	49	56
143-147	22	51	58
148-152	22.5	52.5	60

Angiomax® (bivalirudin) should be administered via an intravenous line. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets. The following drugs should not be administered in the same intravenous line with Angiomax, since they resulted in haze formation, microparticulate formation, or gross precipitation when mixed with Angiomax: alteplase, amiodarone HCl, amphotericin B, chlorpromazine HCl, diazepam, prochlorperazine edisylate, reteplase, streptokinase, and vancomycin HCl. Dobutamine was compatible at concentrations up to 4 mg/mL but incompatible at a concentration of 12.5 mg/mL. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Preparations of Angiomax containing particulate matter should not be used. Reconstituted material will be a clear to slightly opalescent, colorless to slightly yellow solution.

Storage after Reconstitution:
Do not freeze reconstituted or diluted Angiomax. Reconstituted material may be stored at 2-8C for up to 24 hours. Diluted Angiomax with a concentration of between 0.5 mg/mL and 5 mg/mL is stable at room temperature for up to 24 hours. Discard any unused portion of reconstituted solution remaining in the vial.

HOW SUPPLIED

Angiomax® (bivalirudin) is supplied as a sterile, lyophilized product in single-use, glass vials. After reconstitution, each vial delivers 250 mg of Angiomax.

Store Angiomax dosage units at 20-25°C (68-77°F). Excursions to 15-30°C permitted. [See USP Controlled Room Temperature.]
NDC 65293-001-01
Manufactured by:
BenVenue Laboratories
Bedford, OH
Distributed by:
ICS
Louisville, KY
Marketed by:
The Medicines Company
Parsippany, NJ 07054
For information call: (800) 264-4662
U.S. Patent 5,196,404
Rx only

Hemochron® is a registered trademark of International Technidyne Corporation, Edison, NJ.
Revision dated November 29, 2005

PRINCIPAL DISPLAY PANEL
Container Label – 250 mg Vial
NDC 65293-001-01

Angiomax® (bivalirudin)
For Injection
250 mg
For Intravenous Use Only
Rx Only
For Single Use Only

PRINCIPAL DISPLAY PANEL
Package Label – 10-Count Carton, 250 mg Vials
NDC 65293-001-01

Angiomax® (bivalirudin)
For Injection
250 mg
For Intravenous Use Only
Rx Only

Store at 20-25°C (68-77°F).

Excursions to 15-30°C permitted
[See USP Controlled Room Temperature]
Each vial contains 250 mg of bivalirudin with 125 mg of Mannitol and NaOH for pH adjustment. Add 5 mL of Sterile Water for Injection. Each ml contains 50 mg of bivalirudin. For Single Use Only.

Manufactured by:
Ben Venue Laboratories
Bedford, OH

Distributed by:
ICS
Louisville, KY

Marketed by:
THE MEDICINES COMPANY
Parsippany, NJ 07054

10 Single Use Vials


Angiomax®
(bivalirudin)
FOR INJECTION
250 mg
For Intravenous Use Only
Rx Only
10 Single Use Vials
Manufactured by:
THE MEDICINES COMPANY
Parsippany, NJ 07054
Distributed by:
ICS
Manufactured by:
Bar Mills Laboratories
Buford, GA
Each vial contains 250 mg of bivalirudin with 125 mg of Mannitol and NaOH for pH adjustment. Add 5 mL of Sterile Water for Injection. Each mL contains 50 mg of bivalirudin.
Store at 20-25°C (68-77°F)
Excursions to 15-30°C permitted
[See USP Controlled Room Temperature]
10 Single Use Vials
U.S. Patent 5,196,404
Angiomax®
(bivalirudin)
FOR INJECTION
250 mg
For Intravenous Use Only
Rx Only
PN 1401-4
CPS